# "Synthesis, characterization and biological investigation of new bioactive heterocyclic compounds"

**A synopsis submitted to**

## Swami Ramanand Teerth Marathwada University, Nanded (M.S.) India

**For the degree of**

**DOCTOR OF PHILOSOPHY (Ph.D.)**

**IN**

**CHEMISTRY**

**Under the faculty of sciences**

**By**

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Under the Guidance of

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August-2017

# Ph.D. Synopsis

## Subject: Chemistry

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## Title of the Proposed Research Work:

## "Synthesis, characterization and biological investigation of new bioactive heterocyclic compounds"

Heterocyclic compounds are widely distributed in nature and essential to life; they play a vital role in the metabolism of all living cells.Genetic material DNA is also composed of heterocyclic bases-pyrimidines and purines. A large number of synthetic heterocyclic compounds are pharmacologically active and are in clinical use. Heterocyclic compounds have a wide range of application they are predominant among the type of compounds used as pharmaceuticals [1], as agrochemicals and as veterinary products. They also find applications as sanitizers, developers, antioxidants, as corrosion inhibitors, as copolymers, dyestuff [2].

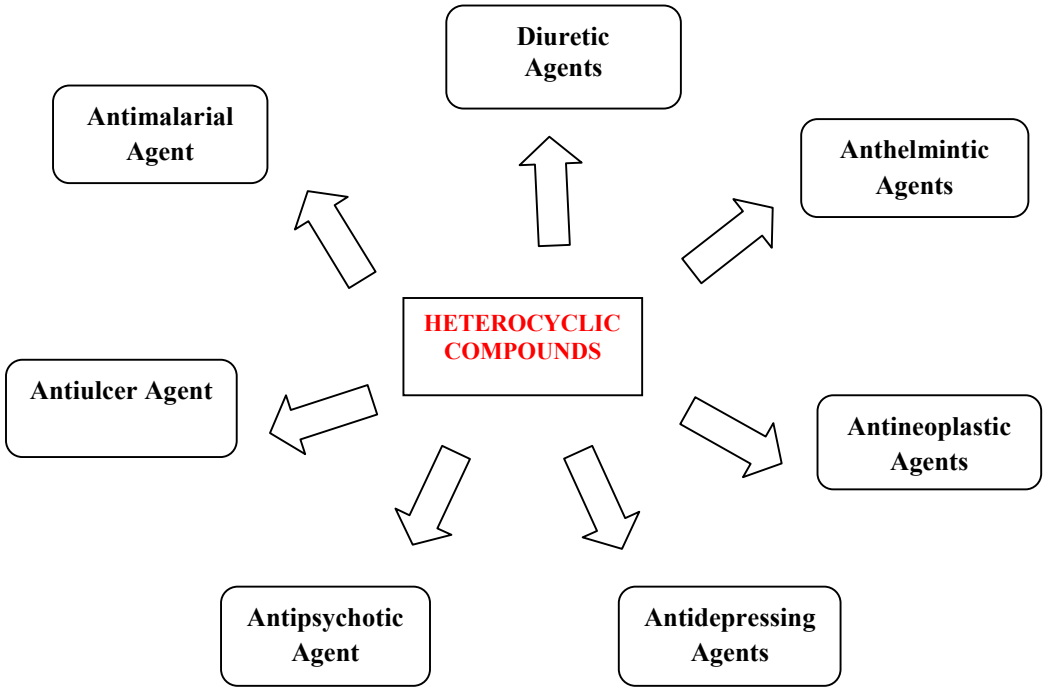
Any of a major class of organic compounds characterized by the fact that some or all of the atoms in their molecules are joined in rings containing at least one atom of an element other than carbon is heterocyclic compounds [3]. The most common heterocyclic like pyridine and pyrrole are prepared by synthetic reactions. Their chief commercial interest lies in their conversion to other substances, chiefly dyestuffs and drugs. Pyridine is used also as a solvent, a waterproofing agent, a rubber additive, and an alcohol denaturant, and a dyeing adjunct [4-5] .Heterocyclic chemistry deals with heterocyclic compounds which constitute about sixty-five percent of organic chemistry literature [6-7].

## Research Problem:

The new era of heterocyclic chemistry is shifting towards the path of innovative techniques which mainly concentrates on environmental aspects [8, 9]. Each and every component of the reaction is investigated on the basis of eco-friendly concepts such as use of nonhazardous solvent (water) and solvent free synthesis or inexpensive catalyst, without affecting the yield and quality of the reaction.

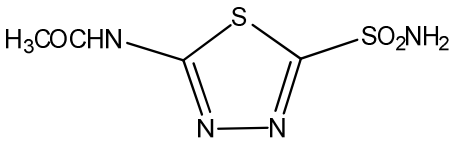
Various methods have been adopted for the synthesis which includes the use of catalyst [10, 11], ultrasound irradiation [12–14], microwave irradiation [15, 16] and also the role of nanocatalyst holds its application [17]. Synthesis of heterocyclic core constitutes the important portion of organic synthesis because it has wide variety of pharmacological actions [18–21].

## Significance of Research Work:



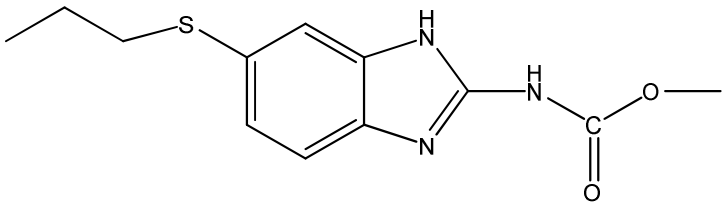
**Heterocyclic compounds as antimalarial:** Chloroquinine, the main drug among the 4-aminoquinoline class, is one of the most successful antimalarial agents ever produced. Prima-quinine is the drug of 8-aminoquinoline class. These amino acid derivatives are known for higher activity and lower toxicity [22].

**Diuretic agents:** Diuretics are medicines that help reduce the amount of water in the body. Acetazolamide is a potent carbonic anhydrase inhibitor, effect in the control of fluid secretion in the treatment of certain Convulsive disorders and in the promotion of diuresis in instances of abnormal fluid retention [23-25].




Acetazolamide

**Anthelmintic:** Helminthic infections contribute to malnutrition, anemia, stunted growth, cognitive impairment, and increased susceptibility to other disseases.Benzimidazole, pyrazine, isoquinoline, tetrahydropyramidine, tetrahydro quinolone, piperidine, piperazine, triazoles, indoleisoxazole derivatives are the different types of heterocycles used as anthelmintics. Albendazole is the most active benzamidazoleanthelminitic drug [26].




Albendazole

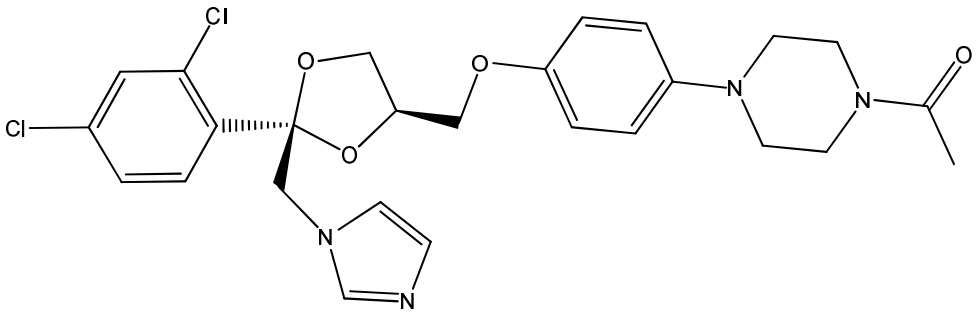
**Antineoplastic agents:** Cancer is a major human health problem worldwide and is the second leading cause of death in United States [27]. Compounds that alkylated DNA have long been of

interest as anticancer drugs. Different types of antineoplastic agents, which include nitrogen mustards (Bendamustine), tyrosine kinase inhibitors, 26S proteasome inhibitors etc. Quinozoline and pyrimidine derivatives are used as tyrosine kinase inhibitors. [28-29]

**Antidepressants:** An antidepressant is a psychiatric medication used to alleviate mood disorders, such as major depression, and dysthymia. Paroxetine, Reboxetine, are some of most useful antidepressants containing heterocyclic moiety in their structure. Some Piperidine and Pyrimidine derivatives also possess antidepressant activity[30-31].

**Antiulcer agents:** Pyridine ring plays an important role in human metabolism due to its interaction with amino acids. Many of the active drugs in the market contain pyridine moiety[32, 33]. Molecules like omeprazole possess gastric antisecretary and consequently anti-ulcerative activity[34]. Later several omeprazole analogues like lanoprazole[35], pantoprazole[36] have been introduced.

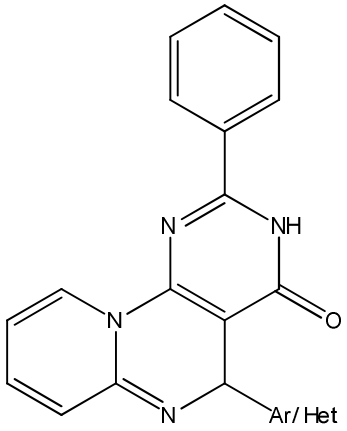
**Antipsychotic agents:** Antipsychotic agents constitute a diverse class of heterocyclic drugs that are effective in the treatment of major psychosis, including those associated with schizophrenia. Benzisoxazole derivatives are found to have antipsychotic properties and are more potent. 3-(piperidin-4-yl)-1, 2-benzisoxazole possess anti-psychotic properties and helpful in the treatment of variety of disorders in which serotonin release is of predominant importance [37]. Some indole derivatives as antiosteoporotic agents [38], and triazole compounds (Fluconazole, Isavuconazole, Hexaconazole, Epoxiconazole, Difenoconazole, Tebuconazole, Ketoconazole etc.,) are used as fungicides[39].



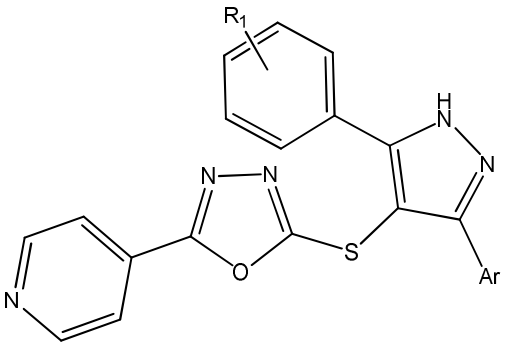

Ketoconazole

Apart from the above significant classes of heterocyclic compounds some derivative useful as therapeutic agents, like 7-hydroxy 4-styryl coumarin showed good antihelmintic activity [40], 2-phenyl 3H-dipyrimido[1,2-a] pyrimidin -4(5H)-one derivatives were screened for their antifungal activity [41],Polyhydroquinoline derivatives were found to be active as antimicrobial agents [42]. bipyrazol-yl-thiazol-ylidene-hydrazinecarbothioamide derivatives were evaluated for their *in vitro* antitubercular activity [43].

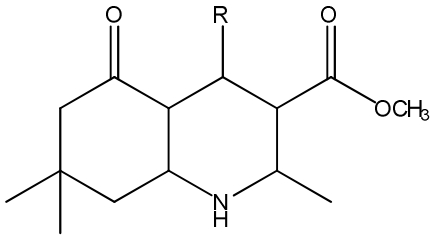
Novel synthesized heterocyclic compounds 2(3,5-disubstituted)-1H-pyrazol-4-yl-thio-5-(pyridin-4-yl)1,3,4-oxadiazoles have shown considerable antioxidant and antimicrobial activity, [44]isoxazolo[4,5-e][1,2,4]triazine derivatives in quantitative yields using PEG-400 were found to be active antibacterial agent [45], indeno-pyrazole derivatives were synthesized act as potent scaffold for designing novel and broad spectrum antimicrobials [46], A new series of dihydro-1H-pyrazolo[3,4-d]pyrimidine and their derivatives were synthesized have good antimicrobial activity [47].



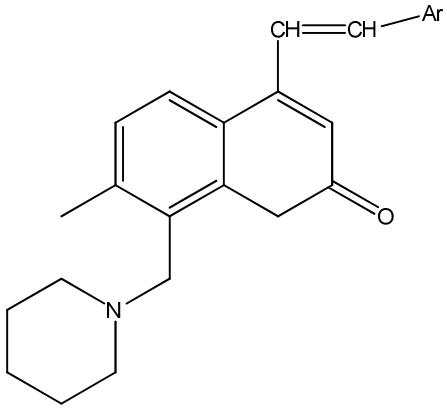

pyrido[1,2-a]pyrimido[5,4-e]pyrimidin-4(5H)-one derivatives




2(3,5-disubstituted)-1H-pyrazol-4-yl-thio-5-(pyridin-4-yl)1,3,4-oxadiazole derivatives




Polyhydroquinoline




7-hydroxy 4-styryl coumarin derivatives

Potential significance of various heterocyclic compounds and their derivatives continue to stimulate research in the area and motivated to opportunity for my research work, because of this I would like to synthesis new bioactive heterocyclic compounds.

## Review of Literature:

After literature survey to the best of our knowledge showed that Heterocyclic chemistry is vastly expanding, because of the enormous amount of research work being done in this area.Heterocyclic chemistry is one of the most interesting, applied branches of organic chemistry and of greatest practical and theoretical importance.

As a result, a great deal of research carried out in chemistry is devoted to heterocyclic chemistry. It is vast and expanding area of chemistry because of obvious application of compounds derived from heterocyclic rings in pharmacy, medicine, biochemistry, medicinal chemistry, dyestuff, photographic sciences, agriculture, insecticide, plastic, polymer, adhesives, molecular engineering and other fields. Heterocyclic compounds are widely distributed in nature. By virtue of their therapeutic properties, they could be employed in the treatment of infectious diseases. Many heterocyclic compounds synthesized in laboratories have been successfully used as clinical agents.

Among the heterocyclic compounds, Thiazoles, Pyrazoles, Imidazole, Quinoxalines, Oxoindolines, Triazoles and Isooxazoles derivatives, are important chemotherapeutic agents and have found wide clinical applications as antimicrobial, anticancer, antiviral and anti-AIDS, antitubercular, sedative/hypnotic/antiepileptic, cardiac agents, as well as analgetics, diuretics, antibiotics and metabolic.

On continuation of our interest to synthesis the heterocyclic compounds, the present work is focused on synthesis of some novel heterocyclic derivatives and to evaluate for their various biological activities.

## Objective of Research Study:

The rate at which heterocyclic compounds continue to be invented testifies to the strength and vitality of this area of medicinal chemistry. Keeping this mind the challenges of discovering new heterocyclic systems and study of their properties and also investigate their applications in medical field.

## Plane of Research Work:

The proposed work will be completed in three phases.

**Phase-I**

In first phase, the extensive collection of references, along with literature survey, synthesis of starting material, intermediate compound and purification solvent will be done.

**Phase-II**

In the second phase maximum attention will be paid on the synthesis and characterization of substituted bioactive heterocyclic compounds on the basic of technique like IR, 1H NMR, 13C NMR, UV Spectral study, Mass Spectroscopy, etc.

**Phase-III**

In this phase focus will be given on biological study and structure activity relationship (SAR) of the synthesized heterocyclic compounds and publication of research work in reputed research journal.

The work carried out under this scheme will be submitted in the form of thesis for the award of Ph.D. degree in chemistry.

## Reference:

1. A. Czarnik, *Acc.Chem.Res, 1996, 29, 112*

2. A. Kozikowski, *Comphrensive Heterocyclic Chemistry, Pergamon Press,1984,1,567*

3. P. Arora, V. Arora, H.S. Lamba& D. Wadhwa;*IJPSR, 2012; Vol. 3(9): 2947-2954*

4. T. Kunied, H. Mutsanga;*The chemistry of heterocyclic compounds, Palmer, B, 2002,175*

5. W.O. Foye, L. Thomas; *Foye's Principles of medicinal chemistry, 2007, 6, 36*

6. L. Bruton, J. Lazo, K. Parker; Goodman & Gilman, *the Pharmacological Basis of Therapeutics,11th edition,972*

7. R. Gupta, M. Kumar, *Heterocyclic Chemistry, 1996, 1, 98*

8. S. M. Roopan& F. R. N. Khan, *Chemical Papers, vol. 64, no. 6, pp. 812–817, 2010.*

9.G. Madhumitha& S. M. Roopan*; Journal of Nanomaterials, vol. 2013, pp. 1–12, 2013.*

10. R. Ghorbani-Vaghei& S. M. Malaekehpoor; *Tetrahedron Letters, vol. 53, pp. 4751–4753, 2012.*

11. K. Rad-Moghadam& S. C. Azimi, *Journal of Molecular Catalysis A, vol. 363-364, pp. 465–469, 2012.*

12. T. S. Jin, J. C. Xiao, S. J. Wang, &T. S. Li, *UltrasonicsSonochemistry, vol. 11, no. 6, pp. 393–397, 2004.*

13. C. L. Ni, X. H. Song, H. Yan, X. Q. Song, & R. G. Zhong, *UltrasonicsSonochemistry, vol. 17, no. 2, pp. 367–369, 2010.*

14. G. Chen, H. Jia, L. Zhang, B. Chen, & J. Li, *UltrasonicsSonochemistry, vol. 20, pp. 627–632, 2013.*

15. A. Lak, M. Mazloumi, M. S. Mohajerani et al., *Journal of the American Ceramic Society, vol. 91, no. 11, pp. 3580–3584, 2008.*

16. M. S. Mohajerani, M. Mazloumi, A. Lak, A. Kajbafvala, S. Zanganeh,&S. K. Sadrnezhaad, *Journal of Crystal Growth, vol. 310, no. 15, pp. 3621–3625, 2008.*

17. R. Narayanan, *Green Chemistry Letters & Reviews, vol. 5, pp. 707–725, 2012.*

18. L. Sang-Bum, P. Young-In, D. Mi-Sook, & G. Young-Dae; *Bioorganic & Medicinal Chemistry Letters, vol. 20, pp. 5900–5904, 2010.*

19. N. M. Sabry, H. M. Mohamed, E. S. A. E. H. Khattab, S. S. Motlaq, & A. M. El-Agrody,*European Journal of Medicinal Chemistry, vol. 46, no. 2, pp. 765–772, 2011.*

20.R. P. Singh, P. Singh, J. Gut, P. J. Rosenthal, & V. Kumar, *European Journal of Medicinal Chemistry, vol. 62, pp. 590–596, 2013.*

21. M. M. Sitonio, C. H. Carvalho Jr., I. A. Campos et al., *Inflammation Research, vol. 62, pp. 107–113, 2013.*

22. I.Puscas, M. Coltan, M. Baican, G. Domuta& A. Hecht*, DrugsExpClin Res. 25(6); 271-279:1992.*

23. Perez Velazquez.*J.Eur J Neurosci. 18(5); 1337-1342:2003.*

24. F. Mincione, A.Scozzafava&C.T.Supuran.,*Curr Pharm Des. 14(7); 649- 654: 2008.*

25. J.Hamzah, T.Skinner-Adams, &T. Davis, *M.E.Acta trop. 74; 39-42: 2000.*

26. L.S.Goodman,M.M. Wintrobe, W. Damesheck, M.J.Goodman, A. Gilman& M.I.Lennan, Mc.*J.Am.Med.Associ. 132; 126:1946.*

27. Louis.J, Lombardo, Francis.Y, Lee, Ping Chen &Derek Norris etal.*J.Med.Chem. 47; 6658-6661: 2004.*

28. J. Zimermann, E. Buchdunger, H. Mett, T. Meya and N. B. Lydon. *Bioorganic &Medicinal Chemistry Letters. 7(2); 187- 192:1997.*

29. F.Holsboer, *Journal of Psychiatric. Research. 33; 1812-1814:1999.*

30. P.J.Gilligan, D.W.Robertson,&R.J.Zaczek, *Med.Chem. 43; 1641-1660: 2000.*

31. Johnson.OandKzons Poland. N.*JL.Chem week. 92 (22); 55: 1963.*

32. Dow.Chem.Co.Neth., Pat.6410223:1963; C.A.,63; 8131:1965.Chapter I; Refer. Page 23

33. R.C. Elderfield,W.J.Genster, J.N. Griffing, T.A.Williamson, S.M. Kupchan, J.T.Maynard, E.J.Kreya andJ.B.Wright, *J.Am.Chem.Soc. 68; 1584:1946.*

34. E. M. Turconi, A. ElicoBellora, A.Brambkca, *Eur.J.Med.Chem. 22; 527: 1987.*

35. A.Nohara, Yi. Maki,*European Patent. 174726:1986.*

36. B.Kohl.etal, European Patent.177287:1986 *J.Med.Chem. 35; 1049:1992.*

37. R. L. Borison, A.P.Patharaja,B.I.Diamond.&Maibach. R.C. *Psychopharmacology Bulletin. 28; 213: 1992.*

38. C. P. Muller, M. D. Collin, B. D. Tan,A. Heather, Y.P.Kharode&T.James. *J.Med.Chem: 44; 1654-1657: 2001.*

39. K. Richardson,*GB Pat 2099818 & US Pat 4404216: 1982.*

40. R. D. Kamble, G. V. Jawadwar, S. D. Patil, S. V. Hese, A. P. Acharya, B. S. Dawane& S. S. Pekamwar*Org. Commun. 6:2 (2013) 95-101.*

41. A. P. Acharya, R. D. Kamble, S. V. Hese, S. N. Kadam , R. N. Gacche and B. S. Dawane, *Org. Commun. 7:2 (2014) 68-76.*

42. P. N. Muli, S. S. Chobe, R. D. Kamble, S. V. Hese, P. P. Mogle, B. S. Dawane, *wjpr, 2014, 3(10), 728-735.*

43. A. N. Ambhore,V. D. Surywanshi, R. D. Kamble, S. V. Hese, P. P. Mogle , S. S. Kadam & B. S. Dawane, *Der PharmaChemica, 2015, 7(4):278-283.*

44. SS.Kadam, P. P. Mogle, A. N. Ambhore, R. D. Kamble, S. V. Hese, S. N. Kadam&B. S. Dawane, *Der Pharmacia Lettre, 2015, 7 (5):73-79.*

45. S. V. Hese, R. D. Kamble, P. P. Mogle, S. S. Kamble , M. J. Hebade, A. N. Ambhore , S. N. Kadam, R. N.Gacche& B. S. Dawane,*JCPRC5 2015, 7(7):784-790.*

46. P. P. Mogle,a R J. Meshram, S. V. Hese, R. D. Kamble, S. S. Kamble, R N. Gacche& B. S. Dawane*Med. Chem. Commun.,2016 DOI:10.1039/C6MD0005A.*

47. A.N.Ambhore, R. D. Kamble, P. P Mogle, S. V. Hese, S. N. Kadam, M. J. Hebade, S. S.Kamble, R. N.Gacche , B. S. Dawane, *Der PharmaChemica, 2017, 9(9):48-56.*

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